

# Chronic Inflammatory Mediators Induced Malignant Changes in Inflammatory Microenvironment of Oral Potentially Malignant Conditions – An Emerging Concept

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**Abstract:** Potentially malignant conditions of the oral cavity are potential threat to mankind because of its malignant changes later. Oral potentially malignant conditions are chronic inflammatory mucocutaneous disorder affecting oral mucosa. Inflammatory mediators induced by chronic inflammatory microenvironment of premalignant conditions are cytokines, chemokines, growth factors, proteolytic enzymes, released by inflammatory cells such as macrophages, lymphocytes, neutrophils, mast cells, activate transcriptional factors such as NF- $\kappa$ B, STAT-3 and HIF-1 $\alpha$ , promotes cell proliferation, angiogenesis, tumor promotion, resistant to apoptosis, epithelial to mesenchymal transition, induced invasion and metastasis. Carcinoma associated fibroblasts in tumor microenvironment originated by activated fibroblasts secretes cytokines and growth factors promotes tumor progression by cell proliferation, angiogenesis, cell survival, genomic instability, invasion and metastasis. Myeloid derived suppressor cells are specialized heterogeneous immature myeloid progenitor cells that are dendritic cells, macrophages, granulocytes produced upon chronic inflammatory mediators. These cells responsible for immune evasion, immunosuppression and tumor progression by various mechanisms and interaction with other immune cells, activating transcriptional factors such as NF- $\kappa$ B and STAT-3. This article describe about roles of chronic inflammatory cells and their mediators in inflammatory microenvironment of premalignant conditions bring about malignant changes in oral sub mucous fibrosis and oral lichen planus.

**Keywords:** MDSC(Myeloid derived suppressor cells), VEGF(Vascular endothelial growth factor), TNF(Tumor necrosis factor), TGF(Transforming growth factor), Oral Submucous fibrosis, Oral Lichen planus, NF- $\kappa$ B, STAT-3, Carcinoma associated fibroblast, Tumor associated macrophage.

## INTRODUCTION

Oral premalignant conditions of oral cavity are also called as oral potentially malignant conditions are chronic inflammatory diseases affecting oral mucous membrane and skin (eg; Lichen planus, oral sub mucous fibrosis). It is a generalised alteration in condition of oral mucosa in which cancer is most likely to occur. Chronic inflammatory mediators in oral potentially malignant conditions, which are responsible for pro- tumoral activity further leads to cancer [1, 2]. Oral submucous fibrosis has a highest rate of malignant potential mainly due to arecanut chewing habit, genetic and infectious agents in some studies, affects oral cavity, pharynx, and upper 1/3rd of esophagus leading to dysphagia and progressive limited mouth opening due to increased production of collagen by fibroblasts. IL-1, TGF- $\beta$ , PDGF, bFGF, cytokines and growth factors stimulate collagen production. IL-1 and TNF- $\alpha$  induced NF- $\kappa$ B transcription factor activation, IL-6 and EGF activates STAT3 transcriptional factor induced by fibroblasts mediated cytokines IL-1, IL-6, IL-8 and TNF- $\alpha$  bring

about cell proliferation, angiogenesis, resistant to apoptosis, invasion and metastasis.

Oral lichen planus is a chronic inflammatory disease of oral mucosa the inflammatory pattern display hallmark of a T-cell mediated disease. Thought to have an autoimmune etiology but no antigen or autoantibodies identified, many studies have showed that it is associated with psychological stress. Lymphocytic and macrophage infiltration in the basal lamina of epithelium is a typical feature, producing inflammatory mediators such as IL-6, TNF- $\alpha$ , IL-1 and IL-8 pro-inflammatory cytokines play a role in malignant transformation [3].

Infectious agents such as microbial stimuli or cellular constituents released upon cell injury and cell death such as (HSp-70 in lichen planus) known as PAMP(Pathogen associated molecular patterns) and DAMP(Damage associated molecular patterns) are recognized by pattern recognition receptors(PRR) belongs to the family of TLR(Toll like receptors) activates innate immunity, results in upregulation of MHC class1 and 11, costimulatory molecules, cytokines, growth factors and chemokines results in activation of key transcription factors such as NF- $\kappa$ B and STAT-3 involved in tumor progression [3,4,1].

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### INFLAMMATORY MICROENVIRONMENT OF ORAL POTENTIALLY MALIGNANT CONDITIONS

The inflammatory mediators in chronic inflammatory microenvironment of oral potentially malignant conditions are IL -1, prostaglandin E2, T lymphocytes, mast cells, TNF- $\alpha$ , TGF- $\beta$ , macrophages, and matrix metalloproteases. Inflammatory cytokines rich microenvironment associated with oral potentially malignant conditions may particularly favorable for tumor promotion [4-8]. Pro- inflammatory cytokine production of IL-1 leads to activation of prostaglandins mediated events via the action of the enzyme cyclooxygenase -2 (Cox-2) an arachidonic acid derivative (Figure 1).

### ROLE OF CHRONIC INFLAMMATORY MEDIATORS IN ORAL POTENTIALLY MALIGNANT CONDITIONS

It has been evidenced that prostaglandins play a significant role in the regulation of local immune response by generation of myeloid derived suppressor cells, as well as carcinogen activation and tumor initiation [9]. Cellular degeneration by Sub epithelial infiltration of T- lymphocytes contributes to the local production of cytokines, which in turn stimulates production of reactive Oxygen species (ROS), reactive nitrogen intermediates (RNI) cause oxidative damage to the tissues. T helper (Th) cells may differentiate into two major subtypes with distinct cytokine profiles and functions in the immune system. Th1 cells typically

produce IFN-  $\gamma$  and TNF- $\alpha$ , which are involved in macrophage activation and play a role in auto-immune diseases associated with chronic infections. The Th17 cytokine is a subset of CD4 T cells produce IL-17, induced by IL-23 pro-inflammatory cytokine is a major mediator of tissue inflammation involved in several autoimmune and inflammatory diseases, activate macrophages, which enhances T cell mediated reactions, inducing production of chemokine's and other pro-inflammatory cytokines such as IL-1 $\beta$ , TNF- $\alpha$ , IL-6 [10, 11]. It has been shown to upregulate and/or synergize with local inflammatory mediators and promote extracellular matrix degradation through stimulating production of MMPs. IL-8 proinflammatory cytokine produced by epithelial cell in an early response of tissue damage, which together with TNF- $\alpha$  and histamine inflammatory mediators secreted by resident macrophages and mast cells allows extravasation of neutrophils to the site of injury results in initiation of inflammation [12].

Chemotactic cytokines are chemokines that involve in migratory and positioning of immune cells to the site of inflammation. Receptors of chemokine's are expressed on all leucocytes produced by stromal and tumor cells, facilitates tumor progression. Neutrophil recruitment is mediated by CXCL1, CXCL2, CXCL3, CXCL5, CXCL6, CXCL7, CXCL8. Recruitment of macrophages and other innate immune cells are by CCL2, CXCL12-CXCR4, CCL4, CCL5, MCP-1.

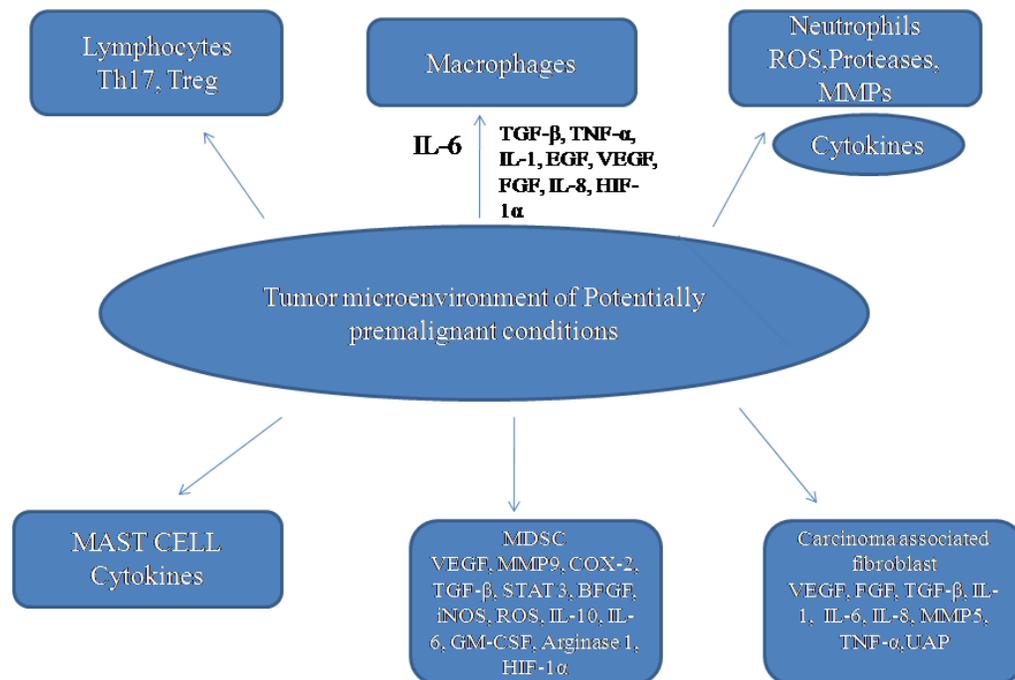


Figure 1: Chronic inflammatory mediators in inflammatory microenvironment of oral potentially premalignant conditions.

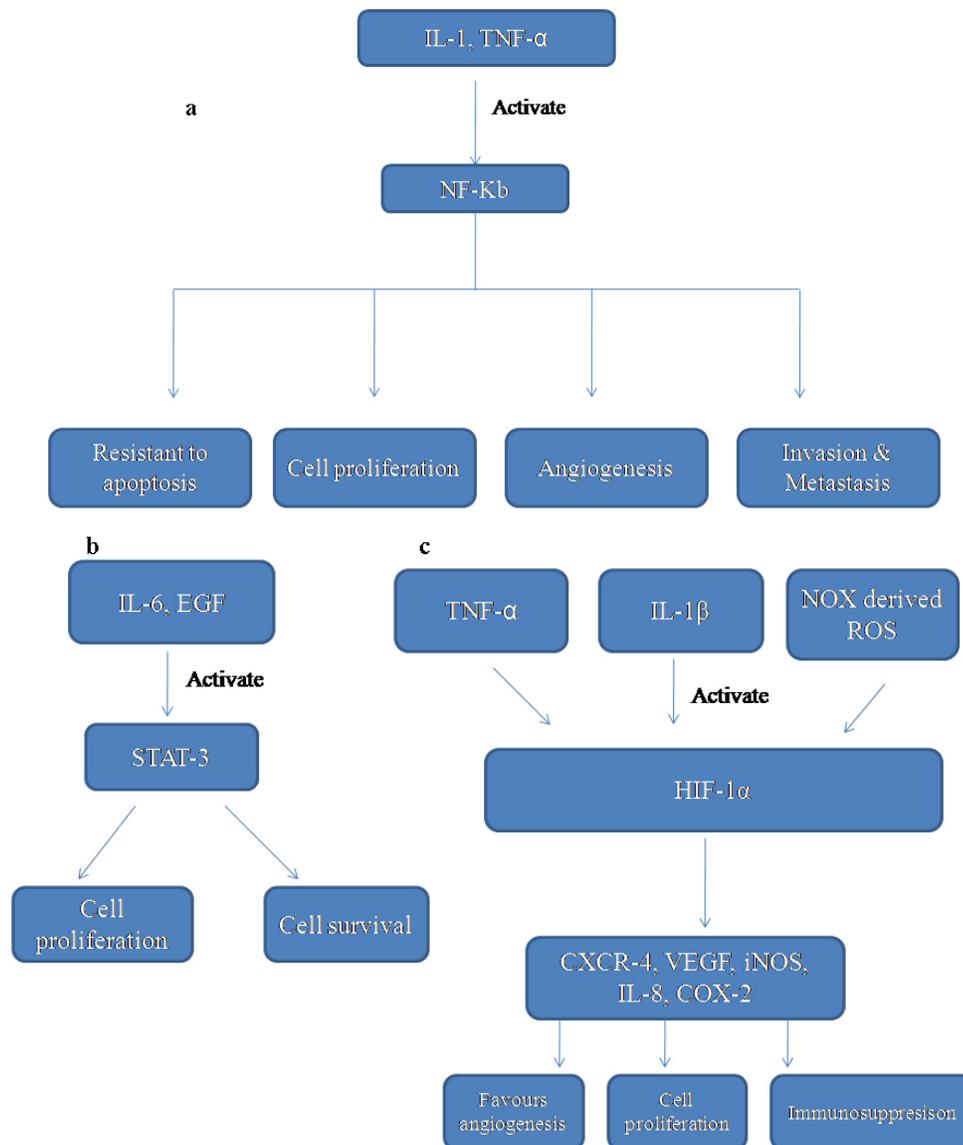
Lymphocytes recruitment by CXCL12-CXCR4, CXCL9, CXCL10, CXCL11, CCR7-CCL21, CXCL19. XCR1 receptors for XCL1(Lymphotactin) expressed on oral cancer cells, keratinocytes and neutrophils, overexpressed on oral cancer cells and in metastatic deposits compared to normal cells on immunohistochemical analysis. Positive staining was seen in an oral potentially premalignant condition called lichen planus with immunological etiology. XCR1 stimulation led to increase in gelatinase MMP2 and MMP9 expression in cancer cells, involve in matrix remodeling and invasion in malignant disease.

Inflammatory factors promoting proliferation are TGF- $\beta$ , FGF (Fibroblast growth factor), and EGF (epithelial growth factor). TGF- $\beta$  is synthesized by mast cells, macrophages, and lymphocytes as an inactive precursor, that is activated by proteases in an inflammatory environment. TGF- $\beta$  promotes mesenchymal cell proliferation and facilitates tumor invasion and metastasis [13, 14]. FGF and EGF are produced by activated macrophages, IL-6 is also produced by tumor associated macrophages, a proliferative factor in cancer, involved in cell proliferation, angiogenesis, and cell survival [15, 16]. Cytokines(IL-8,IL-6,IL-1), Chemokine's (CCL2, CCL4,CCL5, CXCL1 and CXCL8), growth factors(G-CSF, EGF, VEGF, TGF- $\beta$ , GM-CSF) ligands trigger signaling cascades that activates NF- $\kappa$ B, STAT3 transcription factors, promotes cell proliferation, angiogenesis, resistant to apoptosis, epithelial to mesenchymal transition induced invasion and metastasis (Figure 2a, 2b, 2c) [17].

NF- $\kappa$ B is a master regulator of an immune response and important mediator of cell survival by inducing BCL-2 and Bcl-XL protein expression, which in turn triggers expression of pro-inflammatory cytokines, adhesion molecules, and enzymes such as cyclooxygenase 2, matrix metalloproteases 2,9 metalloproteases, iNOS and angiogenic factors favours cell proliferation, angiogenesis, immunosuppression, invasion and metastasis. NF- $\kappa$ B will have a P53 tumor suppressor gene antagonistic activity via expression of AID (Activation induced Cytidine Deaminase) enzyme leads to genomic instability, thereby helps in tumor progression by reducing apoptotic activity of cancer cells results in cancer cells survival. IL-6, EGF, FGF, HGF, PDGF, JAK (janus kinases), tyrosine kinases such as c-met and src activate STAT3 transcription factor work together with NF- $\kappa$ B a key transcription factor involved in chronic inflammation induced tumor initiation, promotion, and progression of oral cancer.

STAT3 transcription factor involved in cell proliferation by induced expression of cyclin D and cell survival by BCL-2 and BCL-XL anti-apoptotic proteins [18, 19]. P13K is also recognized as the main mediator of cell survival in inflammatory microenvironment [20]. Chronic inflammatory cells in inflammatory microenvironment are myeloid derived suppressor cells, macrophages subtypes (M1 and M2), a TIE2-expressing monocyte subset, mast cells, neutrophils, and T and B lymphocytes. These cells secrete chemokine's, prostaglandins, proteases and complement components that collectively bring about an exaggerated inflammatory state, promote cancer growth, angiogenesis, tissue invasion and metastasis [21].

Tumor associated macrophages are functionally and phenotypically divided into two subtypes are M1 phenotype or classically activated macrophages (by Th1 cytokines such as IFN- $\gamma$ ), secrete TNF- $\alpha$ , IL-1, IL-2, IL-6, IL-12 or IL-23 and M2 phenotype or alternatively activated (by Th2 cytokines such as IL-4, IL-13, IL-10) in the tumor microenvironment. M1 macrophages shift towards M2 macrophages secrete TGF- $\beta$  and produce chemokine CCL22 that attracts Treg (Regulatory T cell) cells. Regulatory T cells (Tregs) are main subset of CD4 T cells, express CD25 and FOXP3 involved in immunosuppression by secreting IL-10 and TGF- $\beta$ , suppressing the activity of natural killer (NK) cells, IFN- $\gamma$ , IL-12 and cytotoxic T-cells, which is responsible for immunosuppressive activity and immune evasion. T cell mediated immunosuppression by expression of PD-1 and CTLA-4 receptors on its surface. M2 tumor associated macrophages promote cell proliferation (by IL-1 and IL-6 cytokine production), angiogenesis (by secreting angiopoietins 1 and 2, HIF-1 $\alpha$ , VEGF, GM-CSF, COX-2 and EGF), invasion by secreting proteases (Cathepsin B and D, UPA, MMP -2, 9), Chronic inflammation(by secreting COX-2) and immunosuppression by (iNOS, COX-2, TGF- $\beta$ , IL-10) [21-23]. Interleukin -8 released from the epithelial cells attracts the neutrophils to the inflammatory site in response to oncogenic stress, in tumor microenvironment of oral premalignant conditions. HIF-1 $\alpha$  induced during hypoxic condition by tumor associated macrophages acts as a transcriptional factors for VEGF, IL-1  $\beta$ , and IL-8 favors angiogenesis. Neutrophils are polarized from anti-tumor N1 to a pro-tumoral N2 phenotype, this is regulated by TGF- $\beta$  induced arginase-1 expression [24, 25]. Neutrophils are recruited to the tumor micro-environment secrete



**Figure 2:** Transcription factors activated by inflammatory mediators involved in progression of cancer in potentially premalignant conditions of oral cavity.

prokinectin 2, MMP-9, induce neighbor cells to release VEGF to facilitate the arrival of tumor cells and proliferation by PDGF (Platelet Derived growth factor), thus helps in angiogenesis, tumor growth and metastasis.

B-Lymphocytes secretes IL-10 involved in immunosuppression known as Breg cells regulatory B cells. B-lymphocytes activate mast cells and myeloid cells promotes tumor progression. Mast cells brought to the tumor site by stem cell factor and other inflammatory chemo attractants secretes TNF- $\alpha$ , IL-10, IL-1, and IL-6 cytokines favor tumor growth, angiogenesis and metastasis by secreting angiopoietin-1, VEGF, TGF- $\beta$ , FGF-2 and MMPs. Mast cells recruit eosinophil's, T and B cells induce immune response

and MDSC accumulation in the tumor microenvironment. These cells activates NF- $\kappa$ B through inflammatory mediators, which increases cell survival, suppress T lymphocytes and natural Killer cell cytotoxic activities [26, 27].

Fibroblasts are recruited to neoplastic cells through various cytokines and growth factors. Carcinoma associated fibroblasts are activated fibroblasts in neoplastic cells and form a myofibroblastic microenvironment of potentially malignant conditions of the oral cavity that promotes cell growth, survival and malignancy. Platelet derived growth factor activates fibroblast proliferation secreted by tumor cells. TGF- $\beta$  produced by macrophages acts as chemoattractant at lower concentration, induces differentiation into

myofibroblast at higher concentration. Myofibroblast has a role in cancer invasion and degradation of extracellular matrix and basement membrane through proteases such as urokinase activator of plasminogen Mmp's (Matrix metalloproteases). Myofibroblast express insulin and hepatocytic growth factor, angiogenic growth factors (FGF-2 and VEGF), pro-inflammatory cytokines (IL-1, IL-6, IL-8 and TNF- $\alpha$ ) induces cell proliferation, survival of cancer cells and angiogenesis, thus enhancing tumor invasion, growth, and metastasis (Table 1) [28, 29].

### MYELOID DERIVED SUPPRESSOR CELLS IN CHRONIC INFLAMMATORY MICROENVIRONMENT OF POTENTIALLY MALIGNANT CONDITIONS

Myeloid derived suppressor cells (MDSC) are heterogeneous population of early myeloid progenitors, which includes immature granulocytes, macrophages and dendritic cells upon chronic inflammation [30, 31]. MDSCs can play a role in tumor development by suppressing innate and T cell adaptive immune responses and also promote tumor angiogenesis,

invasion, and metastasis by producing VEGF, basic fibroblast growth factor(bFGF), hypoxic induced factor(HIF)-1 $\alpha$ , TGF- $\beta$  and MMP9 [32]. Inflammatory protein S100A8/A9 produced by MDSCs attracts MDSCs into the tumor site and enhance their immunosuppressive activity but also promote the activation of MAPKs and NF-kB signaling pathways in tumor cells, stimulating tumor growth and metastasis. Activation and expansion of MDSCs is influenced by inflammatory factors released within the tumor microenvironment by tumor and stromal cells are COX2 producing prostaglandins, stem cell factor(SCF), CCL2, GM-CSF, M-CSF, VEGF, CXCL5, calcium binding pro-inflammatory proteins S100A8 and S100A9, TNF- $\alpha$  favors the chemotaxis and expansion of immunosuppressive MDSCs by activating STAT-3 transcriptional factor [33]. The main suppressive activity of MDSCs is associated with secretion of arginase-1, iNOS and ROS. iNOS breaks down L-Arginine into urea and L-ornithine, depleting L-Arginine prevents CD3 generation on T-cells. NO inhibits effector T-cell activation through JAK3 and STAT5 pathways and also abrogate MHC11 molecule

**Table 1: Chronic Inflammatory Mediators and their Role in Inflammatory Tumor Microenvironment of Oral Potentially Malignant Conditions [38-41]**

CYTOKINES	SOURCE	ACTIVATION OF TRANSCRIPTIONAL FACTORS	MECHANISM OF ACTION IN INFLAMMATORY TUMOR MICROENVIRONMENT
IL-1	TAMS, CAFS, Mast cells	NF-KB	Cell proliferation, Angiogenesis, Resistant to apoptosis, Cell survival, Immunosuppression, Epithelial to mesenchymal transition, invasion to metastasis [21]
TNF- Alpha	TAMS, CAFS, Mast cells	HIF - 1 $\alpha$ NF-KB	
IL-6	TAMS, CAFS, Mast cells	STAT-3	Cell proliferation, Cell survival [22]
IL-8	TAMS, CAFS	HIF - 1 $\alpha$	Angiogenesis [23]
TGF- $\beta$	TAMS, CAFS, MDSC		Immunosuppression, Epithelial to mesenchymal transition, Metastasis [23, 28, 24, 25]
IL-17	Th17 cells		Angiogenesis, Immunosuppression, Invasion
GROWTH FACTORS			
FGF	TAMS, CAFS, MDSC		Angiogenesis [29, 23, 31]
EGF	TAMS	STAT-3	Cell survival, Cell proliferation, Angiogenesis [23, 30]
VEGF	TAMS, TAN, MDSC	HIF-1 $\alpha$	Angiogenesis [32, 40, 41]
ENZYMES			
MMPS	TAMS, TANS, MDSC		Invasion and metastasis [40, 22]
COX-2	TAMS	HIF-1 $\alpha$	Angiogenesis, Immunosuppression [23]
UPA	TAMS		Invasion and metastasis [23]

**Abbreviations-**; TAMs; Tumor associated macrophages, CAFs; (Carcinoma associated fibroblasts), MDSC; Myeloid derived suppressor cells, TANs; Tumor associated neutrophils, HIF-1 $\alpha$ ; Hypoxia inducible factor-1Afa.

expression on antigen presenting cells [34, 35]. MDSC mediated immunosuppression is by ROS expression, it is produced by MDSC in response to T-cell interaction or by exposure to cytokines such as TGF- $\beta$ , IL-6, IL-10 and GM-CSF [36]. Hydrogen peroxide is a common form of ROS, prevents cytokine secretion and promotes T-cell apoptosis [37]. In the presence of IFN- $\gamma$  and IL-10, MDSC can induce T-reg cells (Regulatory T cell) expansion by interacting with macrophages, NK cells and NKT cells, thus enhance tumor progression [38-40].

Chronic inflammation induced malignant changes in a potentially malignant conditions of the oral cavity such as lichen planus and OSMF is a complex interactions between immune cells and connective tissue stroma in the inflammatory microenvironment. Chronic inflammatory mediators such as chemokine's involved in the recruitment of inflammatory cells, cytokines, growth factors, proteolytic enzymes activate transcriptional factors secreted by inflammatory cells bring about various changes such as cell proliferation, resistant to apoptosis, angiogenesis, epithelial to mesenchymal transition induced invasion and metastasis still need to be understood thoroughly.

Role of chronic inflammatory cells and their mediators in inflammatory microenvironment of potentially malignant disorders of oral cavity such as oral sub mucous fibrosis, oral lichen planus, involved in tumor initiation, promotion, progression of oral cancer and their signaling pathways need to be studied, which is helpful for drug designing and identification of chronic inflammatory biomarkers for tumor prognosis.

## CONCLUSION AND FUTURE PROSPECTIVE

Chronic inflammatory mediators in microenvironment of oral potentially malignant conditions triggers oncopromotion and oncoprogression by various inflammatory mediators such as macrophages, T lymphocytic cells, and carcinoma associated fibroblasts release cytokines, growth factors and proteolytic enzymes. Myeloid derived suppressor cells are immature myeloid cells present in the inflammatory microenvironment as a result of chronic inflammatory mediators, which promotes immunosuppression, escape immune surveillance and tumor progression. In future perspective, identification of suitable inflammatory biomarkers (such as cytokines IL-6, IL-8, COX2) for early detection of malignancy, therapeutic and prognostic purpose. So, that we can intervene at an

early stage to prevent from progression into malignancy by suppressing inflammation or inflammatory mediators in particular, microenvironment of oral potentially malignant conditions.

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## CONFLICT OF INTEREST STATEMENT

Authors have declared no conflicts of interest.

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## ABBREVIATIONS

HGF	= Hepatic growth factor
VEGF	= Vascular endothelial growth factor
MMP-9	= Matrix mettaloproteinases-9
COX2	= Cyclo-oxygenase2
INOS	= Inducible nitric oxide synthase
ROS	= Reactive oxygen species
PDGF	= Platelet derived growth factor
EGF	= Epidermal growth factor
FGF	= Fibroblast growth factor
TNF-Alfa	= Tumor necrosis factor-Alfa
IFN-Beta	= Interferon Beta
IL-10	= Interleukin 10
TGF-Beta	= Transforming growth factor- Beta
CCL17	= CC Chemokine ligand 17
CCL18	= CC Chemokine ligand 18
CCL22	= CC chemokine ligand 22
PGE2	= Prostaglandin E2
IDO	= Indole amine 2,3-dioxygenase

- UPA = Urokinase plasminogen activator
- UPAR = Urokinase plasminogen activator receptor
- IL-2 = Interleukin 2
- IL-4 = Interleukin 4
- IL-6 = Interleukin -6
- IFN-Gamma = Interferon Gamma
- COX-1 = Cyclo-oxygenase 1
- COX2 = Cyclo-oxygenase 2
- NF-KB = Nuclear factor KB
- MCP-1 = Macrophage/Monocyte chemoattractant protein-1
- M-CSF = Macrophage colony stimulating factor
- IL-17 = Interleukin 17
- CD4+ Th17 = CD4+ T helper lymphocyte17
- MDSC = Myeloid derived suppressor cells
- SR-A = The class A macrophage scavenger receptor msr1
- GM-CSF = Granulocyte Macrophage- Colony stimulating factor
- G-CSF = Granulocyte colony stimulating factor
- STAT3 = Signal transducer and activator of transcription 3
- bFGF = basic fibroblast growth factor
- MMPS = Matrix metallo proteinases
- HIF-1 Alfa = Hypoxia- Inducible factor Alfa
- T reg cell = T regulatory cell
- T h1 = T helper1
- Th2 = T helper 2
- TAM = Tumor associated macrophages
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